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T. Yıldız [a]
S. Gündeş [b,*]
A. Willke [b]
M. Solak [a]
K. Toker [a]
[a] *Department of Intensive Care Unit, Kocaeli University, Dekanlık Binası 41900, Sopalı-Derince, İZMİT, Kocaeli, Turkey*

[b] *Department of Infectious Diseases, Faculty of Medicine, Kocaeli University, Tıp Fakültesi Hastanesi, Dekanlık Binası 41900, Sopalı-Derince, İZMİT, Kocaeli, Turkey*

*Corresponding author. Tel.: +90 262 2335980; Fax: +90 262 2335488/61
E-mail addresses: sgundes@kou.edu.tr sgundes@yahoo.com

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Hemophagocytic syndrome associated with visceral leishmaniasis

Hemophagocytic syndrome (HS) is a clinico-pathologic entity characterized by activation and uncontrolled non-malignant proliferation of T lymphocytes and macrophages. This syndrome, more properly referred to as hemophagocytic lymphohistiocytosis (HLH), is a rare disorder of infancy and early childhood.[1,2] The association of HLH and visceral leishmaniasis (VL) is only rarely found in adults and, when VL and HLH present together in patients, diagnosis of the disease may be difficult.[2,3] Herein, we describe a case of HLH as a complication of VL.

A 34-year-old man was admitted to the Department of Infectious Diseases at Rabta Hospital, Tunis, in May 2003 with a 4-week history of progressive fever accompanied by a marked alteration in his general health, fever, chills, sweats and diarrhea. On physical examination he was found to be febrile (39 °C) and pale. He had hepatomegaly and splenomegaly, but lymph nodes were not enlarged. His vital signs were normal and the rest of the physical examination was unremarkable.

His white blood cell count was 1.89×10^9/L with lymphopenia, anemia and thrombopenia (platelet count, 45×10^9/L). Serum triglycerides were increased to 267 mg/dl with normal cholesterol, and the serum lactate dehydrogenase level was elevated at 1572 U/L. Liver function tests showed alanine amino-transferase (ALT) at 109 U/L and aspartate amino-transferase (AST) at 413 U/L, with alkaline phosphatase at 1169 U/L, and a raised total bilirubin of 17 mg/dl. There was no serological evidence of infection with cytomegalovirus, Epstein—Barr virus or toxoplasmosis. Cultures of blood were negative for specific bacteria. HIV status was unknown because of the fulminant course of the disease.

Initially, the patient received treatment with antibiotics (cefotaxime and ofloxacin), but he continued to have fever with gastrointestinal bleeding and severe pancytopenia, and disseminated intravascular coagulation was diagnosed. The bone marrow aspirate was normal, and bone marrow culture for parasites was negative. However, peripheral blood culture for parasites yielded *Leishmania infantum*, identified as Zymodeme MON 1 at the reference center for leishmaniasis in Montpellier, France.

The patient's condition worsened and he died 2 days later from acute gastrointestinal hemorrhage. Bone marrow biopsy performed after death showed increased monohistiocytes containing phagocytosed erythrocytes, lymphocytes and leukocytes, but no malignancy. These findings, together with clinical presentation and laboratory data, were compatible with a diagnosis of hemophagocytic syndrome. Post mortem findings of liver biopsy showed extensive necrosis with steatohepatitis.

To our knowledge, this is the first report of HLH associated with VL in adults in Tunisia. The diagnostic criteria of HLH proposed by the FHL study group of the Histiocyte Society in 1991,[4] include clinical, laboratory, and histopathologic features. The most common signs are fever and splenomegaly, but hepatomegaly, lymphadenopathy, jaundice, rash and central nervous system manifestations are also seen. Laboratory abnormalities include pancytopenia associated with hypofibrinogenemia, and elevated circulating fibrin degradation products. Most patients have hypertriglyceridemia, elevation of lactate dehydrogenase and marked elevation of ferritin.[1,4]

Histopathologically, hemophagocytosis is seen in bone marrow, spleen, lymph nodes, and occasionally the central nervous system and skin. Our patient had an abnormal coagulation profile, elevated liver enzyme activities, high triglyceride levels, low

plasma fibrinogen levels and bone marrow hemophagocytosis, in keeping with diagnostic criteria of HLH.

Among the numerous causes of reactive hemophagocytic processes, the main ones are lymphomas and viral infections.[3] The first case of VL revealed by a reactive HLH was reported in an adult patient by Matzner et al.[5] The diagnosis of VL may be difficult as clinical signs are similar in both VL and HLH. Furthermore, serologic testing for Leishmania may be negative at the onset of the disease.[1] In a recently reported French series of VL,[6] the parasite was not detected in 22% of cases. The reason for the parasite scarcity in BM smears of patients with VL-associated HLH is unclear. For our patient, Leishmania was isolated only in peripheral blood culture, and BM aspirate was negative for parasites at direct microscopic examination and culture. Thus, diagnostic delays played an important role in the progressive fatal course of our patient's disease.

Several therapeutic protocols are proposed in HLH and depend on the type of hemophagocytic syndrome. In reactive HLH associated with infection, supportive care and specific treatment of the infection are associated with recovery in 60—70% of cases.[7] Thus, the causal therapy of leishmaniasis-associated HLH is based on pentavalent antimonials or amphotericin B, with corticosteroids.[2]

Liposomal amphotericin B seems most suitable for VL-associated HLH, because lipid-associated amphotericin B is taken up by macrophages and targets the drug to the site of infection, leading to very high concentration in the liver and spleen.[1]

Others drugs have been used when HLH is associated with infectious disorders, such as intravenous immunoglobulin, etoposide (which is cytotoxic for macrophages), interferon alpha, corticoids, thalidomide, cyclosporin, cyclophosphamide and antilymphocyte serum.[7]

In conclusion, diagnosis of VL may be difficult, when it is associated with hemophagocytosis. Therefore, leishmaniasis should be considered when discussing the cause of HLH in countries where the disease is endemic, such as Tunisia. Early diagnosis and appropriate treatment of VL are mandatory in order to improve prognosis.

Conflict of interest: No conflict of interest to declare.

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Badreddine Kilani*
Lamia Ammari
Fakher Kanoun
Taoufik Ben Chaabane
Department of Infectious Diseases
Rabta Hospital, Tunis, Tunisia

Sami Abdellatif
Intensive Care Unit, Rabta Hospital
Tunis,Tunisia

Emna Chaker
Department of Parasitology
Rabta Hospital, Tunis, Tunisia

*Corresponding author. Tel.: +216 1 71 57 49 18
fax: +216 1 71 57 49 18
E-mail address: badreddine.kilani@rns.tn
(B. Kilani)

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Coccidioidal pericarditis

We recently presented a case report and review of the literature concerning coccidioidal pericarditis (CP).[1] In all, 17 cases were described. During the time between acceptance of this report and publication an additional patient with CP has been detailed and we believe it would be worthwhile to highlight this case.

A 10 year-old African American girl presented with chest discomfort and dyspnea. She was found to have a left-sided pulmonary infiltrate and a large